REMARKS

I. The Invention

The present invention resides in the novel strategy of *ex vivo* preparation of a tumor-specific vaccine based on the use of bispecific antibodies, which are heterologous intact antibodies of certain isotype combinations. By virtue of its specificities for a tumor-specific antigen, a T cell receptor, and an Fc receptor, a bispecific antibody of the present invention simultaneously binds to a tumor cell (which is an autologous tumor cell extracted from a patient), a T cell, and an Fc receptor-positive effector cell. An enhanced tumor-specific immunity is achieved following the recruitment of T lymphocytes and Fc receptor-bearing effector cells to the tumor cells and the subsequent activation of the T cells and effector cells.

II. The Status of the Claims

Claims 1-26 were originally filed. Claims 27-30 were later added. Upon entry of the present amendment, claims 1-8, 13-21, 23, 26, and 27 remain pending. Claim 1 is amended to recite "at least one tumor-associated antigen on a tumor cell." The support for the term "tumor-associated antigen" can be found throughout the specification, e.g., on page 1 line 20 to page 2 line 2, page 2 lines 18-25, and claims 8 and 12 as originally filed. Claim 6 is amended to correct a typographic error. Claim 14 is amended according to the Examiner's suggestion to address the alleged indefiniteness. The present amendment thus adds no new matter.

III. Claim Rejections

A. 35 USC §103(a) over Volker et al. in View of Deo et al. and Lindhofer et al.

Claims 1-8, 13, 15, 16, 19-21, 23, 26, and 27 were rejected under 35 USC §103(a) for alleged obviousness over Volker et al. in view of Deo et al. and Lindhofer et al. Applicants respectfully traverse the rejections in light of the present amendment.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all elements of a claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the elements; and there must be a reasonable expectation of success in making such combination. MPEP §2143.

Claim 1 as amended is drawn to a method for preparing an antibody-tumor cell preparation and includes the steps of (a) isolating autologous tumor cells; (b) treating the tumor cells to prevent post-reinfusion survival; and (c) incubating the treated tumor cells with intact heterologous bispecific antibodies capable of: (i) binding to a T cell; (ii) binding to at least one tumor-associated antigen on a tumor cell; (iii) binding to an Fc receptor-positive cell via the Fc portion; and (iv) activating the Fc receptor-positive cell whereby the expression of cytokines, co-stimulatory antigens or both is induced or increased. The bispecific antibodies are further limited to the isotype combinations enumerated in claim 1.

The Volker et al. reference discloses methods for inducing an enhanced anti-tumor immunity and for producing a tumor-specific vaccine. These methods require the initial step of antigenizing the tumor cells with an antigen of exogenous origin, e.g., viral protein hemagglutinin-neuraminidase (HN) expressed on the tumor cell surface following the transfection of the tumor cells with the Newcastle Disease Virus (NDV). A bonding agent comprising two bonding components, one of which is capable of binding to the exogenous antigen on the tumor cell surface and the other is capable of binding a molecule on an effector cell surface (such as CD2 or CD3 on a T cell), is then used to bring the effector cell into close contact with the tumor cell and achieve increased immunogenicity of the tumor cells (see column 6 of the Volker et al. patent). Volker et al. describe a recombinantly constructed dual specificity bonding agent that binds tumor cells via an exogenous antigen, e.g., a viral antigen, on the surface of tumor cells. In contrast, claim 1 as amended recites a bispecific antibody capable of binding tumor cells via a tumor-associated antigen. According to the general usage of this term in the art and

as used in the present application (see, e.g., page 1 lines 20-24), an artisan of ordinary skill understands that a "tumor-associated antigen" refers to a tumor cell surface antigen of an endogenous origin, clearly distinguishable from an exogenous antigen, such as a viral protein, present on the cell surface as a result of a viral transfection. Thus, the limitation of a bispecific antibody with specificity to a tumor-associated antigen is not found in the Volker et al. reference. Neither does the Volker reference disclose the limitation of binding to an Fc receptor-positive effector cell, or the isotype combinations recited in claim 1.

The Deo et al. reference relates to recombinant multispecific molecules, which comprise an anti-Fc receptor portion and an anti-target portion, as well as the methods for making and using such molecules. Although the reference describes a molecule of binding specificities for a tumor cell, an Fc receptor, and a cytotoxic T cell (see column 10 lines 24-30 and claim 16), it does not contain all limitations of Applicants' claim 1. Deo et al. describe multispecific molecules that are either M22-based bispecific antibodies, which have an Fab fragment but no Fc region as the anti-Fc receptor portion, or H22-based bispecific antibodies, which have a homologous human IgG1 Fc region as the anti-Fc receptor portion (see, e.g., Example 1 in columns 17-18). The reference thus does not teach an intact heterologous bispecific antibody with an Fc region of claim 1. Moreover, Deo et al. do not teach the isotype combinations recited in Applicants' claim 1.

The Lindhofer et al. reference discloses methods for generating and purifying bispecific rat/mouse antibodies, which demonstrate improved efficiency in producing functional bispecific antibodies and simplified purification procedure. The reference discloses rat/mouse isotype combinations of rat-IgG2a/mouse-IgG2a and rat-IgG2b/mouse-IgG2b, but contains no teaching that a bispecific antibody of such isotype combination may be used to simultaneously recruit and activate T cells and Fc receptor-positive effectors in the close proximity of tumor cells.

When viewed together, it appears that the Volker and Deo references provide the three binding specificities of a bispecific antibody recited in claim 1, and the Lindhofer reference provides some rat/mouse isotype combinations of claim 1. The suggestion to combine the elements necessary for practicing the present invention, however, cannot be found in the references. Specifically, by emphasizing the need to antigenize a tumor cell using an exogenous antigen, the Volker reference does not suggest (if it does not teach away from) using a tumor-associated endogenous antigen for tumor cell binding specificity. One skilled in the art will thus not be motivated to combine the teaching by Volker et al. and Deo et al., since the latter teaches the binding of tumor cells via a tumor-associated antigen. Neither Volker et al. nor Deo et al. suggest an ordinarily skilled artisan to choose any isotype combinations, including the rat/mouse combinations disclosed by Lindhofer et al., to construct the multispecificity antibodies they described. On the other hand, Lindhofer et al. only intended to address the production and purification methods of rat/mouse bispecific antibodies, and not the use of the antibodies to prepare an antibody-tumor cell preparation for immunization of humans and animals against tumor cells. One ordinarily skilled in the art thus will not, after reading the Lindhofer reference, become motivated to use the isotype combinations disclosed in the reference to construct bispecific antibodies according to the teaching of Volker et al. **and** Deo et al. to practice the present invention.

The present invention relies on the novel concept of simultaneous recruitment and activation of T cells and accessory cells in the vicinity of a tumor cell by a bispecific antibody capable of binding all three cells at the same time. As illustrated in the references attached as exhibits to Dr. Lindhofer's declaration (made of record March 15, 2002), the choice of specific subclass combinations is crucial for the successful co-stimulation and activation of T cells and Fe receptor-posititve effector cells, due to the complex nature of cooperation among various types of immune effector cells. See, e.g., right column, page 1246 of Zeidler et al. (*J. Immunol.* **163**:1246-1252, 1999) and right column under the title "DISCUSSION," page 265 of Zeidler et al. (*Brit. J. Cancer*

83:261-266, 2000). Upon reviewing the Volker, Deo, and Lindhofer references cited by the Examiner, one of ordinary skill in the art will not receive any teaching or suggestion relating to the choice of isotype combinations for constructing bispecific antibodies for the purpose of preparing an antibody-tumor cell preparation of the present invention.

In summary, the three cited references provide no suggestion or motivation for an artisan to combine the teaching of the references and arrive at the claimed invention. As such, Applicants submit that *prima facie* obviousness is not established and request that the rejection under 35 USC §103 be withdrawn.

B. 35 USC §103(a) over Honsik et al. in View of Lindhofer et al.

Claims 1-8, 13, 14, 17-21, 23, 26, and 27 were also rejected under 35 USC §103(a) for alleged obviousness over Honsik et al. in view of Lindhofer et al. Applicants respectfully traverse the rejections.

As noted above, an assertion of *prima facie* obviousness is supported when the prior art references supply all claim elements, a motivation/suggestion to combine the elements, and a reasonable expectation of success in combining the elements.

The Honsik et al. reference describes a method for utilizing *ex vivo* IL-2 activation of immune effector cells and arming the activated effectors with monoclonal antibodies whose first binding specificity allows their binding to the effectors and whose second binding specificity allows their binding to an antigen on the surface of the target cells. Applicants' claim 1 requires the use of an antibody that specifically binds to a tumor cell, a T lymphocyte, and an Fc receptor-positive cell simultaneously. The co-stimulation of T cells and accessory cells is an inventive concept of the present invention in that it eliminates the need of exogenous cytokines, e.g., IL2, for activation of the immune effector cells. In contrast, the Honsik reference discloses antibodies capable of simultaneous binding to a target cell and an Fc receptor-bearing effector cell, or simultaneous binding to a target cell and a T cell, but not simultaneous binding to a target

cell, an Fc-receptor positive effector, and a T cell (see, e.g., Abstract, columns 4-5 Brief Summary of the Invention, and Figures 1A-1D of the Honsik reference). The lack of contemplation of simultaneous binding and co-stimulation of multiple immune effector cells by Honsik et al. is further evidenced by their teaching of activation of effector cells with IL2 (see, e.g., Abstract, columns 4-5 Brief Summary of the Invention of the Honsik reference). Thus, Honsik et al. do not expressly disclose or implicitly suggest an antibody with three binding specificities as recited in claim 1 of the present application.

The Lindhofer reference similarly fails to disclose or suggest an antibody capable of simultaneously binding a tumor cell, a T cell, and an Fc receptor-positive cell. As discussed above, a weak anti-tumor immunity is not a problem Lindhofer et al. attempted to address. Rather, the reference discloses nothing more than a method for producing and purifying rat/mouse bispecific antibodies.

When viewed together, the Honsik and Lindhofer references do not supply all limitations of the claimed invention in the present application, namely an antibody that can bind a tumor cell, a T cell, and an Fc receptor-positive effector simultaneously. There is nothing in the Honsik et al. reference that suggests the use of an antibody with an additional specificity for recruiting and activating a second immune effector cell. The reference also offers no disclosure or suggestion regarding the use of any particular isotype combinations (such as the rat/mouse combinations disclosed in the Lindhofer reference) in constructing the bispecific antibodies. The Lindhofer reference, which addresses the production and purification of certain rat/mouse bispecific antibodies, offers no suggestion to the use of a bispecific antibody in an antibody-tumor cell preparation. As such, it cannot be fairly said that one of ordinary skill in the art would be motivated by the Lindhofer reference to introduce to a bispecific antibody as disclosed by Honsik et al. an additional binding specificity for a second immune effector cell, and to construct the bispecific antibodies using the particular isotype combinations.

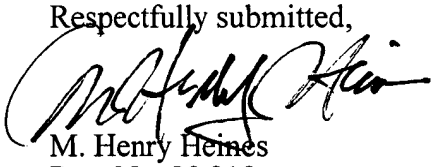
Applicants submit that the Honsik and Lindhofer references do not teach all limitations of claim 1 and provide no suggestion or motivation for combining additional limitations so that one would arrive at the present invention. The rejection of the claimed invention as obvious over the Honsik patent in view of the Lindhofer et al. reference is thus not properly supported. Withdrawal of this rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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